



## **EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion on the substantiation of a health claim related to vitamin D and risk of falling pursuant to Article 14 of Regulation (EC) No 1924/2006**

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## SCIENTIFIC OPINION

### Scientific Opinion on the substantiation of a health claim related to vitamin D and risk of falling pursuant to Article 14 of Regulation (EC) No 1924/2006<sup>1</sup>

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)<sup>2, 3</sup>

European Food Safety Authority (EFSA), Parma, Italy

#### ABSTRACT

Following an application from DSM Nutritional Products Europe AG, submitted pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of the United Kingdom, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver an opinion on the scientific substantiation of a health claim related to vitamin D and risk of falling. Vitamin D (D<sub>2</sub> and D<sub>3</sub>) is sufficiently characterised. A reduction in the risk of falling among men and women 60 years of age and older is beneficial to human health by reducing the risk of bone fractures. Daily vitamin D supplementation (800-1000 I.U.; 20-25 µg) in combination with calcium, when compared to calcium alone, significantly reduced the risk of falling (i.e. risk of falls, risk of falling at least once, or both) in elderly subjects in the five human intervention studies provided by the applicant which had falls as the primary outcome. Statistical pooling of the data from these randomised controlled trials consistently shows a significant reduction in the risk of falling. The available data do not provide information about the lowest effective dose of vitamin D needed to obtain the claimed effect. On the basis of the data presented, the Panel concludes that a cause and effect relationship has been established between the intake of vitamin D and a reduction in the risk of falling. In order to obtain the claimed effect, 800 I.U. (20 µg) of vitamin D from all sources should be consumed daily. The target population is men and women 60 years of age and older. © European Food Safety Authority, 2011.

#### KEY WORDS

Vitamin D, calcium, falls, risk of falling, bone fractures, health claim.

<sup>1</sup> On request from the Competent Authority of the United Kingdom following an application by DSM Nutritional Products Europe AG, Question No EFSA-Q-2010-01233, adopted on 16 September 2011.

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<sup>3</sup> Acknowledgement: The Panel wishes to thank the members of the Working Group on Claims: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Albert Flynn, Ines Golly, Marina Heinonen, Hannu Korhonen, Martinus Løvik, Ambroise Martin, Hildegard Przyrembel, Seppo Salminen, Yolanda Sanz, Sean (J.J.) Strain, Inge Tetens, Hendrik van Loveren and Hans Verhagen for the preparatory work on this scientific opinion.

## SUMMARY

Following an application from DSM Nutritional Products Europe AG, submitted pursuant to Article 14 of Regulation (EC) No 1924/2006 via the Competent Authority of the United Kingdom, the Panel on Dietetic Products, Nutrition and Allergies was asked to deliver an opinion on the scientific substantiation of a health claim related to vitamin D and risk of falling.

The scope of the application was proposed to fall under a health claim referring to disease risk reduction.

The Panel considers that the food constituent, vitamin D (D<sub>2</sub> and D<sub>3</sub>), which is the subject of the health claim, is sufficiently characterised.

The claimed effect is “reduces the risk of falling. Falling is a risk factor for fractures”. The target population proposed by the applicant is men and women 60 years of age and older. The Panel considers that a reduction in the risk of falling among men and women 60 years of age and older is beneficial to human health by reducing the risk of bone fractures.

A total of seven randomised controlled trials (RCTs), five observational studies and four meta-analyses were submitted as being pertinent to the claim.

Three meta-analyses included only part of the individual RCT considered as pertinent by the applicant and do not provide any additional information for the scientific substantiation of the claim. A randomised, double-blind, placebo controlled intervention tested the effects of a combination of calcium plus vitamin D without controlling for calcium intake. The Panel considers that no conclusions can be drawn from these references for the scientific substantiation of the claim.

Five RCTs showed a significant reduction in the risk of falling (i.e. risk of falls, risk of falling at least once, or both) of elderly subjects consuming vitamin D supplements daily (800-1000 I.U.; 20-25 µg) in combination with calcium compared to calcium alone. One other RCT was unable to demonstrate an effect of daily vitamin D supplementation (200-800 I.U.; 5-20 µg) on the risk of falling in elderly nursing home residents, although the study may have been underpowered in relation to that outcome as the primary outcome was vitamin D status. Statistical pooling of the data from these RCTs consistently shows that daily vitamin D supplementation at doses of 800-1000 I.U./day (20-25 µg/day) in combination with calcium significantly reduces the risk of falling compared to calcium alone. The Panel considers that the available data do not provide information about the lowest effective dose of vitamin D needed to obtain the claimed effect.

The Panel considers that results from the observational studies provided are inconsistent and residual confounding cannot be excluded.

Regarding the mechanisms by which vitamin D could exert the claimed effect, three RCTs showed an effect of vitamin D supplementation on body sway, muscle function and strength, or both, together with a significant reduction in the risk of falling. No consistent association was observed between vitamin D status and muscle strength in the observational studies provided. The Panel notes that, although plausible, the relationship between vitamin D intake or vitamin D status and muscle strength, physical performance and balance in the elderly is yet to be established.

In weighing the evidence, the Panel took into account that daily vitamin D supplementation (800-1000 I.U.; 20-25 µg) in combination with calcium when compared to calcium alone significantly reduced the risk of falling (i.e. risk of falls, risk of falling at least once, or both) in elderly subjects in the five human intervention studies provided by the applicant which had falls as the primary outcome, and that statistical pooling of the data from these RCTs consistently shows a significant reduction in the risk of falling.

The Panel notes that all the studies which showed an effect of daily vitamin D supplementation on the risk of falling used supplemental calcium in combination. However, since physiological functions of calcium (except bone mineralisation) are unrelated to dietary calcium intake level, the Panel considers that it is unlikely that supplemental calcium is required for an effect of vitamin D on the risk of falling.

On the basis of the data presented, the Panel concludes that a cause and effect relationship has been established between the intake of vitamin D and a reduction in the risk of falling.

The Panel considers that the following wording reflects the scientific evidence: “Vitamin D may reduce the risk of falling. Falling is a risk factor for bone fractures”.

The Panel considers that, in order to obtain the claimed effect, 800 I.U. (20 µg) of vitamin D from all sources should be consumed daily. The target population is men and women 60 years of age and older.

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## BACKGROUND

Regulation (EC) No 1924/2006<sup>4</sup> harmonises the provisions that relate to nutrition and health claims, and establishes rules governing the Community authorisation of health claims made on foods. As a rule, health claims are prohibited unless they comply with the general and specific requirements of this Regulation, are authorised in accordance with this Regulation and are included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Articles 14 to 17 of this Regulation lay down provisions for the authorisation and subsequent inclusion of reduction of disease risk claims and claims referring to children's development and health in a Community list of permitted claims.

According to Article 15 of this Regulation, an application for authorisation shall be submitted by the applicant to the national competent authority of a Member State, which will make the application and any supplementary information supplied by the applicant available to the European Food Safety Authority (EFSA).

## STEPS TAKEN BY EFSA

- The application was received on 13/10/2010.
- The scope of the application was proposed to fall under a health claim referring to disease risk reduction.
- The scientific evaluation procedure started on 15/11/2010.
- On 28/01/2011, the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application and the clock was stopped on 01/02/2011 in compliance with Art. 16(1) of the Regulation (EC) No 1924/2006.
- On 26/05/2011, EFSA received the requested information as submitted by the applicant and the clock was restarted.
- During the meeting on 16/09/2011, the NDA Panel, after having evaluated the overall data submitted, adopted an opinion on the scientific substantiation of a health claim related to vitamin D and risk of falling.

## TERMS OF REFERENCE

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16 of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA will issue an opinion on the scientific substantiation of a health claim related to: vitamin D and risk of falling.

## EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation to the marketing of vitamin D, a positive assessment of its safety, nor a decision on whether vitamin D is, or is not, classified as a foodstuff. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

It should also be highlighted that the scope, the proposed wording of the claim, and the conditions of use as proposed by the applicant may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 17 of Regulation (EC) No 1924/2006.

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<sup>4</sup> European Parliament and Council (2006). Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. Official Journal of the European Union OJ L 404, 30.12.2006. Corrigendum OJ L 12, 18.1.2007, p. 3–18.

## INFORMATION PROVIDED BY THE APPLICANT

**Applicant's name and address:** DSM Nutritional Products Europe AG, Peter Merian Haus, Peter Merian-Strasse 80, 4052 Basel, Switzerland.

### Food/constituent as stated by the applicant

According to the applicant, Vitamin D in its variant forms vitamin D<sub>3</sub> and vitamin D<sub>2</sub>.

### Health relationship as claimed by the applicant

According to the applicant, Vitamin D is an essential micronutrient with a role on muscle function. The applicant states that vitamin D has a role in preventing falling in the elderly, and that this effect may be mediated via muscle function. The applicant also states that falling is a risk factor for fractures.

### Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim: "Vitamin D reduces the risk of falling. Falling is a risk factor for fractures".

### Specific conditions of use as proposed by the applicant

The target population for the intended health claim is men and women 60 years of age and older. An additional intake of 700-1000 I.U./day (17.5-25 µg/day) is required to achieve the claimed effect (i.e. in addition to baseline dietary intake in the intended population).

## ASSESSMENT

### 1. Characterisation of the food/constituent

The food constituent that is the subject of the health claim is vitamin D, which is a well recognised nutrient and is measurable in foods by established methods. Vitamin D occurs naturally in foods as vitamin D<sub>2</sub> (ergocalciferol) and vitamin D<sub>3</sub> (cholecalciferol). Different forms of vitamin D are authorised for addition to foods and for use in food supplements (Annex II of the Regulation (EC) No 1925/2006<sup>5</sup> and Annex II of Directive 2002/46/EC<sup>6</sup>). This evaluation applies to vitamin D<sub>2</sub> and D<sub>3</sub>, which are authorised forms for addition to foods and for use in food supplements (Annex II of the Regulation (EC) No 1925/2006 and Annex II of Directive 2002/46/EC).

The Panel considers that the food constituent, vitamin D (D<sub>2</sub> and D<sub>3</sub>), which is the subject of the health claim, is sufficiently characterised.

### 2. Relevance of the claimed effect to human health

The claimed effect is "reduces the risk of falling. Falling is a risk factor for fractures". The target population proposed by the applicant is men and women 60 years of age and older.

<sup>5</sup> Regulation (EC) No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods. OJ L 404, 30.12.2006, p. 26–38.

<sup>6</sup> Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements. OJ L 183, 12.7.2002, p. 51–57.

A claim on calcium and vitamin D and the reduction of the risk of osteoporotic fractures by reducing bone loss pursuant to Article 14 of Regulation (EC) No 1924/2006 has been already assessed with a favourable outcome (EFSA, 2009). At least 1200 mg of calcium from all sources or at least 1200 mg of calcium and 800 I.U. (20 µg) of vitamin D from all sources to be consumed daily were proposed in order to obtain the claimed effect (EFSA, 2010a). The target population was women 50 years and older.

Postural instability and muscle weakness are positively associated with the risk of falling (Horlings et al., 2008). A fall can be defined as “the unintentional coming to rest on the ground, floor, or other lower level”. Approximately 5 % of falls in the elderly result in bone fracture, the most common age-related bone fractures being in the wrist, spine, hip, humerus and pelvis (Tinetti et al., 1988). In community dwelling older people, 25 % of age-related fractures are in the hip and 95 % of hip fractures are caused by falls (Skelton and Todd, 2004).

The number of falls in a population subgroup over a period of time can be recorded and results expressed as, e.g. the number of falls per person per observation time (incidence), the total number of falls or the number of subjects falling at least once. The Panel notes that the risk (and relative risk) of falls and of falling at least once, which can be calculated from these variables, are appropriate outcome measures for the assessment of the risk of falling in human intervention studies.

The Panel considers that a reduction in the risk of falling among men and women 60 years of age and older is beneficial to human health by reducing the risk of bone fractures.

### **3. Scientific substantiation of the claimed effect**

The literature search by the applicant was performed using PubMed and using the search terms (“vitamin D” OR ergocalciferol OR cholecalciferol) AND (falls OR falling). The limits were set to include only human clinical trials, randomised controlled trials and meta-analyses published in English. The search was performed on March 25, 2010, and yielded 73 publications. Seventeen other relevant publications were found by hand searching. In total 90 publications were considered. The applicant considered as not pertinent to the application publications in which vitamin D was not included in the intervention, was not evaluated as an independent variable, was part of a multiple intervention with nutrients other than calcium, was administered as vitamin D analogue or using a route other than oral, or was given with a frequency less than monthly; falls were not an endpoint, were not defined, or were not correctly measured; the target population was not the general elderly population (e.g. frail or very ill elderly); statistical analyses could not adequately correct for confounding factors (e.g. subjects unequally distributed at baseline). Detailed reasons for exclusion of each individual study were provided in the application.

A total of seven randomised controlled trials (RCTs), five observational studies and four meta-analyses were submitted as being pertinent to the claim. The Panel notes that three of the meta-analyses provided (Bischoff-Ferrari et al., 2004; Jackson et al., 2007; Gillespie et al., 2009) included human intervention studies which were not considered as pertinent by the applicant for one or more of the following reasons: use of food constituents not relevant to the present application (i.e. calcitriol), use of routes of administration (i.e. parenteral) not relevant to human nutrition, lack of a definition for falls, enrolment of frail elderly. In addition, all these meta-analyses included only part of the individual RCT considered as pertinent by the applicant and do not provide any additional information for the scientific substantiation of the claim. The Panel considers that no conclusions can be drawn from these meta-analyses for the scientific substantiation of the claim.

The individual RCTs are described below, followed by one meta-analysis of RCTs and five observational studies.



### *Randomised controlled trials*

A randomised, double-blind, placebo controlled, 3-year intervention, in which self-recorded falls were the primary outcome, was undertaken in 445 free-living men and women aged 65 years and older (Bischoff-Ferrari et al., 2006). Subjects were randomly assigned to receive 700 I.U. (17.5 µg) vitamin D<sub>3</sub> plus 500 mg calcium or placebo daily. The Panel notes that this study tested the effects of a combination of calcium plus vitamin D without controlling for calcium intake and that the study design does not allow conclusions to be drawn on the effects of vitamin D alone. The Panel considers that no conclusions can be drawn from this study for the scientific substantiation of the claim.

A short-term randomised, double-blind, controlled intervention (eight weeks, running from March until May) was undertaken by Pfeifer et al. (2000) in which 148 free-living women (mean age 74 years) with serum 25(OH)D concentrations <50 nmol/L were given 800 I.U. (20 µg) vitamin D<sub>3</sub> plus 1200 mg calcium (D + Ca) or 1200 mg calcium (Ca) daily. Women were followed-up for one year (uncontrolled) after the end of the intervention. A total of 145 women completed the intervention, whilst 67 women in the Ca and 70 women in the D + Ca group completed the one-year follow-up. Falls were recorded by questionnaires during the intervention and follow-up and were defined as falling onto the floor or ground or hitting an object like a chair or stair. Body sway was measured at baseline and at the end of the intervention by using a sway meter that measured displacements of the body in frontal and sagittal direction at the level of the waist in 30-s periods. The sway area was calculated by multiplying the frontal with the sagittal diameters. Primary outcomes of the study were changes in secondary hyperparathyroidism and body sway between groups. The authors state that to prove a difference of 50 % of the SD with a power of 80 %, 74 subjects per group were needed, but the outcome measure used to calculate sample size is not reported. Between-group differences were assessed using two-sided unpaired t-tests for independent samples or the Mann-Whitney U test. Statistical analyses were performed in the ITT (intention to treat) population. Both the intervention and control groups had higher serum 25(OH)D concentrations at the end of the eight-week intervention compared to baseline (baseline values for the D + Ca and Ca groups=25.65±12.14 nmol/L and 24.63±12.14 nmol/L, respectively), but these were significantly higher in the D + Ca group compared to the Ca group (increase from baseline=+40.46±27.01 nmol/L vs. +18.30±20.94 nmol/L; p=0.0001). Body sway sagittal diameter was significantly reduced at 8 weeks in the D + Ca group compared to the Ca group (p=0.0435), whereas no significant differences between groups were observed in body sway frontal diameter or in body sway area. In comparison with the Ca group, the D + Ca group had a smaller number of participants who fell (11 and 19, respectively, p=0.0373) and a lower total number of falls (17 and 30, respectively, p=0.03546) at one year follow up. However, the Panel notes that these crude comparisons did not take into account the sample size of the intervention and placebo groups. The Panel notes that the relative risk (RR) of falls was significantly lower in the D + Ca group relative to the Ca group (17 falls in 70 subjects vs. 30/67, RR=0.54, 95% CI: 0.33-0.89), whereas no statistically significant differences were observed with respect to the relative risk of falling at least once (11/70 subjects falling at least once vs. 19/67, RR=0.55, 95% CI: 0.29-1.06). However, the Panel also notes that both RRs are similar, and that this study may not have been adequately powered to detect a significant difference between groups in relation to the risk of falling at least once, which appears to be a more conservative estimate than the risk of falls.

Bischoff et al. (2003) conducted a randomised, double-blind, controlled intervention from November to March in 122 women aged at least 60 years (mean age 85.3 years, range 63-99 years) living in long-stay geriatric care units in Switzerland. These women were at high risk of vitamin D deficiency, physical frailty, muscle weakness and falls. Women were randomised to 800 I.U. (20 µg) vitamin D<sub>3</sub> + 1200 mg calcium (D + Ca) or 1200 mg calcium (Ca) daily for 12 weeks. Falls were recorded by nurses for six weeks before and for 12 weeks during the intervention and were defined as unintentionally coming to rest on the ground, floor or other lower level. Musculoskeletal function was assessed by the summed score of knee flexor and extensor strength, grip strength, and the timed up and go test at baseline and at the end of the intervention. A total of 44 subjects per group was

calculated to detect a difference of 43 % in the number of falls between groups with  $\alpha=0.05$  and a power of 90 %. The planned study population was 120 subjects to allow for a 30 % drop out rate. Of the 122 women randomised (62 to the D + Ca and 60 to the Ca group), 89 completed the study (45 in the D + Ca and 44 in the Ca group). Statistical analyses for falls were carried out on an ITT basis. At study entry, 50 % of women had 25-hydroxyvitamin D serum concentrations  $<30$  nmol/L, 90 %  $<78$  nmol/L, and 95 %  $<100$  nmol/L. Seventeen percent of subjects met the criteria for secondary hyperparathyroidism, namely increased intact parathyroid hormone (iPTH) levels (iPTH  $\geq 55$  pg/ml) and normal serum calcium levels. At baseline there were no differences between the groups in the number of falls per person. A significant increase in serum 25(OH)D was observed in the D + Ca group [median interquartile range from 30.75 (23.0-55.0) nmol/L to 65.5 (49.75-82.75) nmol/L, +71 %] compared to the Ca group [from 29.0 (23.0-55.0) nmol/L to 28.5 (24.5-61.25), -4 %,  $p<0.0001$ ]. The D + Ca treatment showed a significant reduction in falls (RR=0.68, 95 % CI: 0.14-0.71,  $p=0.01$ ) after adjustment for age, number of falls pre-treatment, being a faller in the pre-treatment period, baseline concentrations of 25(OH)D, and observation time during treatment. The crude t-test comparing the mean number of excessive falls (number of falls during treatment minus number of falls pre-treatment) among fallers during the treatment period was significantly lower in the D + Ca group than in the Ca group ( $p=0.045$ ), suggesting a decrease in recurrent falls in the D + Ca group. The number of fallers did not differ significantly between groups (RR of falling at least once=0.7; 95 % CI: 0.3-1.5). In the 62 women who completed baseline and follow-up measures (per-protocol (PP) analysis), a significant ( $p=0.0094$ ) improvement in skeletal muscle function was observed in the D + Ca group compared to the Ca group. The Panel notes that a daily vitamin D supplement of 800 I.U. (20  $\mu$ g) in combination with calcium significantly reduced the risk of falls in recurrent fallers compared to calcium alone, and that this effect was accompanied by a significant improvement in skeletal muscle function.

Flicker et al. (2005) conducted a randomised, double-blind, controlled, multicentre (60 assisting living facilities and 89 nursing homes across Australia) intervention in 625 elderly (80 years or older, 95 % women) living in residential care. Subjects were randomised within each institution in blocks of eight to consume 1000 I.U. (25  $\mu$ g) vitamin D<sub>2</sub> plus 600 mg calcium (D + Ca) or 600 mg calcium (Ca) daily for 2 years. Baseline 25(OH)D was  $<60$  nmol/L in 89 % of participants and  $<40$  nmol/L in 57 %. Falls were recorded in diaries during the intervention and were defined as an event that results in a person coming to rest inadvertently on the ground or other lower level. After recruitment was complete, and based on the observed fall rates for both groups (the investigators were still blinded), a revised recruitment target of 620 subjects was chosen based on the study having 80 % power to detect a difference in the proportion of fallers of 11 % and an 18 % change in the falls rate ( $\alpha=0.05$ ). Statistical analyses were performed ITT and PP by excluding subjects with a pre-defined compliance  $<50$  % (assessed by pill count). The effect of the intervention on serum 25(OH)D concentrations was not measured. On the ITT analysis, there was a significant reduction in the incidence of falls in the group receiving D + Ca compared to the Ca group (665 falls in 486 person years vs. 890 falls in 478 person years). The incidence ratio of the D + Ca group compared with the Ca group was 0.73 (95 % CI: 0.57-0.95). In the PP analysis (i.e. 85 participants with compliance  $<50$  % were excluded from the analysis) the effect of vitamin D<sub>2</sub> was more pronounced, with an incidence ratio of 0.63 (95 % CI: 0.48-0.82). The RR of falling at least once (170/313 subjects in the D + Ca group vs. 185/312 in the Ca group, RR=0.92, 95 % CI: 0.80-1.05) was not significantly different between groups. The Panel notes that this study showed an effect of vitamin D and calcium compared to calcium alone in reducing the incidence of falls, whereas no significant difference was observed with respect to the risk of falling at least once.

Prince et al. (2008) undertook a 1-year double-blind, RCT in 302 free-living older women (70-90 years) with serum 25(OH)D concentrations  $<60$  nmol/L at baseline. Women were randomised to receive 1000 I.U. (25  $\mu$ g) vitamin D<sub>2</sub> plus 1000 mg calcium (D + Ca) or 1000 mg calcium (Ca) ( $n=151$  per group). The randomisation procedure used a random number generator with a block size of 10 to assign participants to vitamin D or placebo in a ratio of 1:1, thus ensuring equal recruitment to the two

groups during the various seasons. Falls were defined as unintentionally coming to rest on the ground, floor or other lower level and were recorded on a questionnaire during the six weeks previous to the intervention, and every six weeks during the intervention by the staff via telephone or clinic visit interview. Based on the estimation that at least one fall a year would have occurred in 60 % of the study population, 113 subjects per group were needed to detect a 37 % reduction in the RR of falling at least once with  $\alpha=0.05$  and a power of 90 %. Statistical analyses were performed on an ITT basis. Follow-up was incomplete for 15 women in the D + Ca group and for 12 women in the Ca group. Eighty subjects (53.0 %) in the D + Ca group and 95 subjects (62.9 %) in the Ca group had at least one fall (OR=0.66; 95 % CI: 0.41-1.06), so that the RR of falling at least once was not significantly different between groups. However, after adjusting for height (which was an independent predictor of falling, was positively correlated with muscle strength after adjusting for age and weight, and was significantly lower in the D + Ca than in the Ca group at baseline), the D + Ca group had a significantly lower risk of falling at least once based on ITT analysis (OR=0.61, 95% CI: 0.37-0.99). Eighty-three patients (47 %) had one fall and 92 (53 %) had >1 fall during the study. The percentage of subjects who sustained multiple falls was not significantly different between groups. According to an explanatory analysis in which first falls were grouped according to season, vitamin D<sub>2</sub> treatment reduced falling in winter and spring, when serum 25(OH)D concentrations were 28 % higher in the D + Ca group than in the Ca group (<50 nmol/L in the Ca group), but not in summer and autumn, when serum 25(OH)D concentrations were 12.5 % higher in the D + Ca group than in the Ca group (>50 nmol/L in the Ca group). The Panel notes that this study showed that intake of vitamin D and calcium reduced the risk of falling at least once compared to calcium alone, whereas no significant effect was observed on the number of multiple fallers.

Pfeifer et al. (2009) undertook a 1-year double-blind, RCT in 242 free-living elderly subjects (three quarters of whom were females,  $\geq 70$  years of age) with serum 25(OH)D concentrations <78 nmol/L. Participants were either given 800 I.U. (20  $\mu$ g) vitamin D<sub>3</sub> plus 1000 mg calcium (D + Ca) or 1000 mg calcium (Ca) daily for 12 months (n=121 per group), with an additional 8-month treatment-free, blinded follow-up. Falls (primary outcome) were defined as in Pfeifer et al. (2000) and were self-recorded by participants during the 20 months of the study. Secondary endpoints were assessed at baseline, at the end of the intervention and at the end of follow-up and included isometric leg extensor strength, body sway total path length, timed up and go test scores, and serum 25(OH)D concentration. Statistical analyses were carried out on an ITT basis. PP analyses excluded 31 subjects due to compliance <80 % or loss on follow up. Total falls were 171 in the Ca group and 76 in the D + Ca group. Over the 20-month period, 63 % of the Ca group had at least one fall compared to 40 % in the D + Ca group ( $p<0.001$ ). The mean number of falls per person was 1.41 in the Ca group and 0.63 in the D + Ca group ( $p<0.001$ ). A 27 % reduction in the RR of falling at least once was observed in the D + Ca group as compared to the Ca group at month 12 (RR=0.73; 95 % CI: 0.54-0.96;  $p<0.01$ ) and a 39% reduction was observed at month 20 (RR=0.61; 95 % CI: 0.34-0.76;  $p<0.01$ ). Isometric leg extensor muscle strength was significantly higher in the D + Ca group at months 12 and 20, whereas timed up and go test scores and body sway total path length were significantly lower in the D + Ca group at months 12 and 20, and at month 20 only, respectively, compared to the Ca group. The Panel notes that a daily supplement of 800 I.U. (20  $\mu$ g) vitamin D<sub>3</sub> for one year reduced the risk of falling at least once in elderly men and women living in the community for up to 8 months after the discontinuation of the supplement, and that this reduction was associated with an increased muscle strength.

Broe et al. (2007) conducted a 5-month randomised, double-blind, placebo controlled intervention study in 124 elderly nursing home residents (75 % female, mean age 89 years, age range 68-104 years), who were randomised in blocks of 15 to one of the five study groups [placebo, 200 I.U. (5  $\mu$ g), 400 I.U. (10  $\mu$ g), 600 I.U. (15  $\mu$ g) or 800 I.U. (20  $\mu$ g) of vitamin D<sub>2</sub>/day] using a computer-generated randomisation list (23 to 26 subjects per group). Sixty-three percent were taking a daily multivitamin, average serum 25(OH)D concentration was  $48.75 \pm 24.75$  nmol/L, and 62 % had fallen in the previous year. Of those taking a multivitamin at baseline, 54 % had serum 25(OH)D concentrations  $\leq 50$

nmol/L. The study was designed to assess the effect of different doses of vitamin D on vitamin D status (primary outcome for power calculations), and then used to test the effect of vitamin D on falls. Falls were defined as a sudden, unintentional change in position causing a resident to fall on the ground and were recorded by nurses during the study. A total of 114 subjects completed the 5-month intervention (loss of one to three subjects per group). Data analysis was carried out in the ITT population. Over 5 months, 61 of 124 (49 %) participants had at least one fall; 11 of 25 (44 %) experienced a fall in the placebo group, 15 of 26 (58 %) in the 200 I.U. group, 15 of 25 (60 %) in the 400 I.U. group, 15 of 25 (60 %) in the 600 I.U. group, and five of 23 (22 %) in the 800 I.U. group. No significant difference was observed in the risk of falling at least once between any of the groups and no linear trend was observed across groups. No significant differences were observed with respect to the incidence of falls between the placebo group and any of the vitamin D groups. Among participants with valid follow-up 25(OH)D measures (n=100), the 800 I.U. (20 µg) group had a mean follow-up 25(OH)D concentrations of  $74.88 \pm 14.65$  nmol/L, compared to mean values ranging from 55 to 60 nmol/L in the other four groups. All subjects in the 800 I.U. group had serum 25(OH)D concentrations >50 nmol/L. The Panel notes that the risk of falling at least once was not significantly different for any dose of vitamin D intake compared to placebo, that no dose-response was observed with respect to this outcome measure, and that no significant effect was observed on the incidence of falls. However, the Panel also notes that this study may have been underpowered with respect to these outcomes variables (i.e. the primary outcome was vitamin D status).

The Panel notes that five RCTs showed a significant reduction in the risk of falling (i.e. risk of falls, Pfeifer et al., 2000, Bischoff et al., 2003, Flicker et al 2005; risk of falling at least once, Prince et al., 2008; or both, Pfeifer et al., 2009) of elderly subjects consuming vitamin D supplements daily (800-1000 I.U.; 20-25 µg) in combination with calcium compared to calcium alone. The Panel also notes that one other RCT (Broe et al., 2007) was unable to demonstrate an effect of daily vitamin D supplementation (200-800 I.U.; 5-20 µg) on the risk of falling in elderly nursing home residents, although the study may have been underpowered in relation to that outcome as the primary outcome was vitamin D status.

The Panel considers that daily vitamin D supplementation (800-1000 I.U.; 20-25µg) in combination with calcium when compared to calcium alone significantly reduced the risk of falling in elderly subjects in the five human intervention studies provided by the applicant which had falls as the primary outcome.

#### *Meta-analysis of randomised controlled trials*

A meta-analysis of RCTs (Bischoff-Ferrari et al., 2009) which aimed to investigate the efficacy of supplemental vitamin D with or without calcium in preventing falls among older individuals was also provided. The meta-analysis included eight RCTs (Bischoff-Ferrari et al., 2006; Pfeifer et al., 2000; Bischoff et al., 2003; Flicker et al., 2005; Broe et al., 2007; Prince et al., 2008; Pfeifer et al., 2009; Graafmans et al., 1996), one of which had four intervention arms (Broe et al., 2007). All these studies except Graafmans et al. (1996) have been described above. The outcome measure of efficacy used was the risk of falling at least once. All studies provided enough data for the calculation of the RR of falling at least once in the vitamin D group (+/- Ca) relative to the control group. The meta-analysis included 2426 participants, 81 % of whom were women, approximate mean age 80 years. Vitamin D supplementation was significantly associated with a reduced risk of falling at least once (RR=0.87, 95% CI: 0.77-0.99), although heterogeneity in results was observed among studies (Q test: p=0.05). When the analysis was stratified by daily dose of vitamin D ("low"=200-600 I.U. vs. "high"=700-1000 I.U.), the "high" vitamin D dose significantly reduced the risk of falling by 19 % (pooled RR=0.81, 95 % CI: 0.72-0.92) whereas the "low" dose had no effect (pooled RR=1.10, 95 % CI: 0.89-1.35). Serum 25(OH)D concentrations of 60 nmol/L or more resulted in a 23 % fall reduction (pooled RR=0.77, 95% CI: 0.65-0.90), whereas lower 25(OH)D concentrations were not significantly associated with the risk of falling at least once (pooled RR=1.35, 95 % CI: 0.98-1.84).



The Panel notes that only the study by Graafmans et al., (1996) and three intervention arms from the study by Broe et al. (2007) were used to assess the effects of “low” (200-600 I.U./day, 5-15 µg/day) vitamin D doses on the risk of falling (n=505 subjects vs. n=1921 subjects included in the assessment of higher vitamin D doses), that the study by Broe et al. (2007) was not designed to assess the effects of vitamin D on the risk of falling and may have been underpowered for that outcome, and that the study by Graafmans et al. (1996) was excluded by the applicant due to methodological limitations. The Panel considers that no conclusions can be drawn from this meta-analysis with respect to the effect of vitamin D supplementation at doses of 200-600 I.U./day (5-15 µg/day) on the risk of falling. The Panel also notes that no dose-response was observed in this meta-analysis for vitamin D intake or vitamin D status with respect to the risk of falling (IoM, 2010).

With respect to the effect of vitamin D supplementation at “high” doses (700-1000 I.U./day, 17.5-25 µg/day), the Panel notes that the meta-analysis included one RCT (Bischoff-Ferrari et al., 2006) which used a combination of vitamin D plus calcium without controlling for calcium intake was considered to be not pertinent to the present application. However, the Panel also notes that exclusion of this study from the analysis still results in a significant effect of vitamin D supplementation at doses of 800-1000 I.U./day (20-25 µg/day) on the risk of falling (RR=0.83; 95 % CI: 0.75-0.92), even when possible publication bias was taken into account using the Copas model (RR=0.85; 95 % CI: 0.75-0.96). Exclusion of the study by Broe et al. (2007) from the analysis did not significantly change the results.

The Panel notes that statistical pooling of the data from the RCTs described above as being pertinent to this application consistently shows that daily vitamin D supplementation at doses of 800-1000 I.U. (20-25 µg) in combination with calcium significantly reduces the risk of falling compared to calcium alone. The Panel considers that the available data do not provide information about the lowest effective dose of vitamin D needed to obtain the claimed effect.

#### *Observational studies*

In a prospective cohort study conducted in Australia (Flicker et al., 2003) 667 older women in low-level (hostels) care (mean serum 25(OH)D=39.7±20.3 nmol/L) and 952 women in high-level (nursing homes) care (mean serum 25(OH)D=31.4±19.7 nmol/L) were followed up for an average of 145 and 168 days, respectively (mean age 83.7 years). Falls were recorded in diaries by the staff. Overall, 97 % of all women had a serum 25(OH)D <50 nmol/L, and 22 % in low-level care and 45 % in the nursing homes had a serum 25(OH)D <25 nmol/L, but only 8 % of residents in hostels and 4 % in nursing homes were receiving vitamin D supplementation. A total of 388 falls were recorded in 177 (27 %) women in low-level care and 643 falls were recorded in 238 (25 %) women in high-level care, yielding average ± standard error falls rates of 1.6±0.2 falls/year and 1.5±0.1 falls/year, respectively. The median time to first fall was 44 and 43 days, respectively. Survival analysis (Cox proportional hazards model) for time to first fall was performed excluding the 358 women who were bed bound. After adjustment for variables which were significantly associated with the risk of falling in univariate analyses (body weight, past Colles fracture, being a wanderer, neuroleptic medication, worse cognition), serum 25(OH)D remained independently and inversely associated with the risk for falling (hazard ratio=0.74; p<0.01). It was estimated that doubling serum 25(OH)D concentrations would result in a 20 % reduction in the risk of falling. The Panel notes that this study shows an inverse association between vitamin D status and the risk of falling in older women living in low- and high-level care institutions.

In a 5-year prospective cohort study (Snijder et al., 2006), 1231 Dutch men and women aged 65-85 years who were either free-living or in a nursing home were asked to record falls in a calendar which was mailed weekly to the investigators. Proxies (persons in the same household, carers) were contacted if participants were not able to respond. After adjusting for confounders (i.e. age, sex, education level, region, season, physical activity, smoking, and alcohol intake), 25(OH)D concentrations <25 nmol/L were significantly associated with a higher risk of falling: two falls or

more, OR=1.78 (95 % CI: 1.06-2.99); three falls or more, OR=2.23 (95 % CI: 1.17-4.25). No significant differences in the risk of falling were observed between different categories of serum 25(OH)D concentrations >25 nmol/L. The Panel notes that this study shows an association between 25(OH)D concentrations <25 nmol/L and an increased risk of recurrent falls in older subjects living in the community or in nursing homes.

Faulkner et al. (2006) recorded self-reported vitamin D supplementation (at least once weekly) and falls over a 4-year period in 9526 free-living US women with a mean age of 70 (interquartile range=67-75) years. Incident fall rates (number of falls/woman-years) were used as main outcome variable. In a subset of 389 women out of 400 which were randomly selected from the cohort, serum 25(OH)D and 1,25(OH)D concentrations, grip and quadriceps strength, chair-stand time, walking speed, reaction time, and balance-walk time (including changes in grip strength, chair-stand time, walking speed and balance-walk time over approximately 3.7 years) were also assessed. Consumption of vitamin D supplements was reported by 44.9 % of women at baseline. Over a mean follow-up period of 3.8 years, 17450 falls were reported for a mean annual fall rate of 482 falls per 1000 women (95 % CI: 476-490). In the subset of 389 randomly selected women, statistics for median age, vitamin D supplement use, and annual fall rates were nearly identical to those for women from the total cohort (70 years, 44.8 %, and 459 falls per 1000 women, respectively). This subset of women was also comparable to the entire cohort for a wide range of clinical variables (e.g. anthropometrics, physical activity, cognitive impairment, muscle strength and function). After adjusting for potential confounders, no significant effect of vitamin D supplementation on fall rates was observed in the subsample of 389 women (456 falls per 1000 woman-years among non-current users of vitamin D supplements compared to 519 falls per 1000 woman-years among current users). There was neither a significant trend nor a threshold association between serum 25(OH)D and fall rates. However, a higher 1,25(OH)D concentration was associated with a lower fall rate in the multivariate model ( $p=0.039$ ). The mean (interquartile range) serum 25(OH)D concentration was 68 (53-85) nmol/L in the supplement users and 55 (43-70) nmol/L in the non-users. The Panel notes that supplement use was self-reported but the significant difference in mean serum 25(OH)D concentrations between users and non-users ( $p<0.001$ ) validates the accuracy of the reporting. The Panel notes that although vitamin D supplements were not associated with lower fall rates in this study, a higher serum 1,25(OH)D concentration was associated with a lower fall rate, indicating that the efficiency of conversion of 25(OH)D to the active form, 1,25(OH)D, may be important for the effect. Overall, no association was found between vitamin D supplementation, 1,25(OH)D or 25(OH)D concentrations and any measure (or changes in any measure) of neuromuscular function in any statistical model, with the exception of 1,25(OH)D concentrations and faster chair-stand time and 25(OH)D concentrations and grip strength. The Panel notes that, overall, this study did not show an association between vitamin D supplementation or status and neuromuscular function.

Lloyd et al. (2009) prospectively measured the rate of recurrent falls (self-reported) in 193 free-living elderly (mean age=81±8 years) men and women during the year after a hip fracture. Mean serum 25(OH)D concentrations were significantly higher in the non-fallers/single fallers (mean, 95 % CI=49.0, 37.0-65.3 nmol/L) than in the recurrent fallers (mean, 95 % CI=38.0, 21.3-64.3 nmol/L; OR=0.13, 95 % CI: 0.03-0.69,  $p=0.02$ ). It was calculated that for every 10 nmol/L increase in serum 25(OH)D concentrations there was an 87 % decrease in recurrent fall risk and the risk of all “all fall-related injuries”. In simple regression analyses, serum vitamin D was significantly correlated with muscle strength and static balance. The Panel notes that, in multivariate analyses taking into account other risk factors for falls (e.g. medications, chronic diseases, quality of life), vitamin D status was not independently associated with recurrent falls in this study. The Panel considers that this study does not show an independent association between vitamin D status and falls in the free-living elderly after a hip fracture.

In a prospective cohort study (Pramyothin et al., 2009) 495 postmenopausal, community dwelling, women of Japanese ancestry living in Hawaii were asked to self-report falls for 2 years and 8 months. No significant relationship was observed between serum 25(OH)D concentrations and incidence of

one or more falls. Among performance-based measures, activities of daily living, and strength tests (grip, triceps, quadriceps), only quadriceps strength was significantly associated with 25(OH)D concentration. The Panel notes that this study did not show an association between vitamin D status and risk of falling but that the 25(OH)D concentrations were relatively high in this population subgroup (mean±SD=79.9±23.7 nmol/L), with only 44 % of the sample being <75 nmol/L.

The Panel notes that one prospective cohort study in elderly women reported an inverse association between vitamin D status and the risk of falling (Flicker et al., 2003) and that another showed an increased risk of recurrent falls in elderly men and women with low serum 25(OH)D concentrations (Snijder et al., 2006). The Panel also notes that no effect of vitamin D supplements on fall rates was found in another study (Faulkner et al., 2006), although higher 1,25(OH)D concentrations were associated with fewer falls, which indicates that the efficiency of conversion of vitamin D supplements may confound the relationship between vitamin D intake and falls. No independent association between vitamin D status and falls in single or recurrent fallers was observed in free-living elderly during the year after a hip fracture (Lloyd et al., 2009) and no association was found between 25(OH)D concentrations and risk of falling in post-menopausal Japanese women with relatively high vitamin D status (Pramyothin et al., 2009). The Panel considers that the results from the observational studies provided are inconsistent and that residual confounding cannot be excluded.

#### *Mechanisms of action*

Regarding the mechanisms by which vitamin D could exert the claimed effect, the applicant acknowledges that there is a paucity of human data apart from muscle function and body balance. Three RCTs showed an effect of vitamin D supplementation on body sway (Pfeifer et al., 2000), muscle function and strength (Bischoff et al., 2003) or both (Pfeifer et al., 2009) together with a significant reduction in the risk of falling. No consistent association was observed between vitamin D status and muscle strength in the observational studies provided. The Panel notes that, given the well established role of vitamin D on muscle function (EFSA, 2010b), an improvement in muscle function, strength and body balance could be a plausible mechanism by which vitamin D could exert the claimed effect. However, the relationship between vitamin D intake or vitamin D status and muscle strength, physical performance and body balance in the elderly is yet to be established (e.g. Latham et al., 2003; Annweiler et al., 2009).

In weighing the evidence, the Panel took into account that daily vitamin D supplementation (800-1000 I.U.; 20-25 µg) in combination with calcium when compared to calcium alone significantly reduced the risk of falling (i.e. risk of falls, risk of falling at least once, or both) in elderly subjects in the five human intervention studies provided by the applicant which had falls as the primary outcome, and that statistical pooling of the data from these RCTs consistently shows a significant reduction in the risk of falling.

The Panel notes that all the studies which showed an effect of daily vitamin D supplementation on the risk of falling used supplemental calcium in combination. However, since physiological functions of calcium (except bone mineralisation) are unrelated to dietary calcium intake level, the Panel considers that it is unlikely that supplemental calcium is required for an effect of vitamin D on the risk of falling.

The Panel concludes that a cause and effect relationship has been established between the intake of vitamin D and a reduction in the risk of falling.

#### **4. Panel's comments on the proposed wording**

The Panel considers that the following wording reflects the scientific evidence: "Vitamin D may reduce the risk of falling. Falling is a risk factor for bone fractures".

## 5. Conditions and restrictions of use

In order to obtain the claimed effect, 800 I.U. (20 µg) of vitamin D from all sources should be consumed daily. The target population is men and women 60 years of age and older.

## CONCLUSIONS

On the basis of the data presented, the Panel concludes that:

- The food constituent, vitamin D (D<sub>2</sub> and D<sub>3</sub>), which is the subject of the health claim, is sufficiently characterised.
- The claimed effect proposed by the applicant relates to the reduction in the number of fallers and falls. The target population proposed for the claim is men and women 60 years of age and older. A reduction in the risk of falling among men and women 60 years of age and older is beneficial to human health by reducing the risk of bone fractures.
- A cause and effect relationship has been established between the intake of vitamin D and a reduction in the risk of falling.
- The following wording reflects the scientific evidence: “Vitamin D may reduce the risk of falling. Falling is a risk factor for bone fractures”.
- In order to obtain the claimed effect, 800 I.U. (20 µg) of vitamin D from all sources should be consumed daily. The target population is men and women 60 years of age and older.

## DOCUMENTATION PROVIDED TO EFSA

Health claim application on vitamin D and risk of falling pursuant to Article 14 of Regulation (EC) No 1924/2006 (Claim serial No: 0291\_UK). November 2010. Submitted by DSM Nutritional Products Europe AG.

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**GLOSSARY / ABBREVIATIONS**

|      |                             |
|------|-----------------------------|
| iPTH | Intact parathyroid hormone  |
| ITT  | Intention to treat          |
| OR   | Odds ratio                  |
| PP   | Per-protocol                |
| RCT  | Randomised controlled trial |
| RR   | Relative risk               |